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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,619	BJORN ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *7,24,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-23,25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/13/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 22 has been amended, claim 26 has been cancelled and claim 29 has been added as per Applicant's amendment dated January 11, 2005.

Claims 1-25 and 27-29 are currently pending.

Applicant's election of Group I, claims 1-25 and 29, drawn to compositions of the formula A-(LM)-C, and the species of Phe-Phe-Arg chloromethly ketone as a FVIIa inhibitor, an immunoglobulin Fc as element "C", and SEQ ID NO:14 $(GGGGS)_n$ as the "LM" moiety, and a listing of the claims to which these elections are generic in the reply filed on January 11, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 27 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 7 and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species as indicated in Applicant's response dated January 11, 2005, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 11, 2005.

It is noted that applicant's response indicates that claims 7 and 9 are distinct species with regard to element "C". However, claim 9 is not seen as a distinct species

by the examiner since the elected species of an Fc region is found within an immunoglobulin as recited in claim 9. Also, Applicant indicated that claims 23 and 24 are drawn to species of "LM" moieties distinct from the elected species. However, the examiner has considered claim 23 to be part of the elected "LM" species since it recites an element that is generic for a peptide.

Claims 1-6, 8-23, 25, and 29 are under examination as they read on Phe-Phe-Arg chloromethly ketone as a FVIIa inhibitor, an immunoglobulin Fc as element "C", and SEQ ID NO:14 $(GGGGS)_n$ as the "LM" moiety in compounds of the general formula A-(LM)-C.

Applicant's form 1449 filed Nov. 13, 2003 is acknowledged. Three references have been crossed out because they are duplicates.

Specification

2. Applicant's amended sequence listing has been acknowledged.

The specification is objected to because it has not yet been amended to indicate that the sequence $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$ that appears in the specification on page 15, line 15, is SEQ ID NO:14. Appropriate amendment to the specification is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 5-6, 8, 10, 20, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Garen, (WO 01/02439 A1, see entire document).

Garen teaches therapeutic immunoconjugates consisting of a targeting domain consisting of FVII and an effector domain consisting of the Fc region of IgG1 (see entire document particularly page 1, lines 1-15). The targeting domain contains FVII that is a mutated form of FVII that binds with high affinity and specificity to tissue factor (TF) but does not initiate blood coagulation (see particularly page 1, lines 12-14). The human IgG1 effector domain mediates a cytolytic response against target cells by natural killer cells (NK) and the complement pathways of the immune system (see particularly the paragraph that spans pages 10 and 11). Since TF is expressed by endothelial cells of the neovasculature and by many tumor cells, a therapeutic reagent that targets such cells is useful in the treatment of vascularized tumors (see particularly lines 17-20 of page 4). The immunoconjugate of Garen is a dimmer that allows for the interaction of the compound with more than one molecule of TF (see particularly page 4, lines 6-17, and claim 1). The form of FVII used in the immunoconjugate of Garen is human FVII

that has one or more amino acid substitution mutations in the active site that remove the protease activity of FVII (see particularly page 4, lines 10-17, and claims 2-3). Such mutations are needed since the binding of the immunoconjugate to TF could lead to disseminated intravascular coagulation unless the enzymatic activity of FVII is removed (see particularly gage 11, lines 11-25). Since both the FVII and IgG1 domains are of human origin, immune rejection responses in human patients are minimized (see particularly page 11, lines 23-25). The immunoconjugate of Garen can be administered as a purified protein in conjunction with pharmaceutically acceptable carriers or excipients (see particularly page 5, lines 2-3). The immunoconjugate of Garen was also able to inhibit TF-mediated FVIIa activity as measured by a competitive binding assay and by *in vivo* data showing decreased tumor vasculature in tumor challenged mice (see particularly Examples 2 and 3, most particularly the paragraph that spans pages 28 and 29 and Figures 4-12).

The immunoconjugate composition of Garen consists of the zymogen, FVII, rather than the activated form, FVIIa. The zymogen form of FVII used by Garen is fully capable being cleaved *in vivo* to generate FVIIa, although it would be an inactive form of FVIIa due to the mutation in the active site. Such a form of the immunoconjugate was formed in the mice used in Examples 2 and 3 of Garen. The immunoconjugate of Garen does not contain a linker moiety that joins FVII to the Fc domain, but this is an optional limitation of the claims as currently recited.

Therefore, the prior art anticipates the claimed invention.

5. Claims 1, 2, 5, 6, 8, 9, 14, 15, 20, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Soule et al. (U.S. Patent No. 5,506,134, see entire document).

Soule et al. disclose monoclonal antibodies that are specific for the blood factors VII and VIIa (see entire document, particularly the abstract). These antibodies are neutralizing, and bind FVII, FVIIa, FVII and FVIIa, or TF/FVIIa (see particularly column 7, lines 9-28 and the paragraph that spans columns 11 and 12). These monoclonal antibodies were screened for their ability to bind ^{125}I labeled factor VII *in vitro* (see particularly from column 12, line 55 to column 13, line 5). As such, Soule et al. generated a compound that consisted of FVII non-covalently bound to an immunoglobulin molecule. Soule et al. used human FVII or FVIIa in conducting their experiments (see particularly the paragraph that spans columns 5 and 6, and column 12, lines 33-45).

One particular antibody isolated by Soule et al., 12D10, was found to be specific for the catalytic domain of FVII, and this antibody is capable of binding FVII before and after formation of FVII/TF complexes (see particularly column 15, lines 15-18). As such this antibody is specific for FVII and does not inhibit FVII/TF complex formation. This antibody also inhibits the activity of both FVIIa and FVIIa/TF complexes (see particularly Table 4 in column 14). Soule et al. further disclose that their antibodies are to be used in the prevention and treatment of diseases (see particularly the abstract and column 1, lines 15-22). The antibodies of Soule et al. have two antigen binding domains, and as such they can bind two FVII molecules. Each FVII molecule attached to the antibody can independently associate with TF, and thus the composition of Soule et al.

comprises more than one binding site for TF. The antigen-antibody binding experiments disclosed by Soule et al. in Examples 1-6 were carried out in buffers and solutions that were not toxic to cells (see particularly Example 2). Therefore, the compounds containing an antibody bound to FVII disclosed by Soule et al. were present in a pharmaceutically acceptable carrier or excipient.

As such, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 3, 4, 16, 17, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garen, (WO 01/02439 A1, see entire document) as evidenced by Capon et al. (US Patent No. 5,565,335, see entire document), in view of Sorensen et al. (J. Biol. Chem. 1997, 272:11863-11868, see entire document).

The teachings of Garen have been discussed above. These teachings differ from the claimed invention in that FVII is inactivated by mutating the sequence of FVII rather than using an inhibitory peptide or small organic compound.

Sorensen et al. teach that the affinity of human FVIIa for TF is increased if the active site of FVIIa is blocked with the irreversible inhibitor D-Phe-L-Phe-L-Arg chloromethyl ketone (see entire document, particularly the abstract, the final paragraph of the Introduction on page 11863, and the paragraph that spans the left and right columns of page 11866). The increase in affinity gained by using active site inhibited FVIIa was 5-fold for non-functional tissue factor sites as compared to unmodified FVIIa, whereas the affinity of inhibited and uninhibited FVIIa for functional tissue factor sites was comparable (see particularly the abstract). The increased affinity of FVIIa inactivated with the peptide for binding to TF as compared to the binding of native FVIIa is due to conformational structural differences as determined by spectroscopy (see particularly Figures 7-8 and the last full paragraph of page 11867). The enhanced affinity of active site inactivated FVIIa for TF allows for the use of low concentrations of active site inactivated FVIIa that function as an effective anticoagulant and reduce TF-

induced thrombus formation (see particularly the paragraph that spans pages 11867 and 11868).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the FVIIa that has been catalytically inactivated using a peptide as taught by Sorensen for the amino acid sequence mutated inactive form of FVII taught in the immunoconjugate of Garen. Motivation to make this substitution comes from the teaching of Sorensen et al. that FVIIa that has been inactivated using a peptide has a conformation that allows for higher affinity interactions with TF. Since the FVII of the immunoconjugate of Garen is used as a targeting molecule to deliver the composition to tumor and tumor vascular cells that express TF, a form of FVII that has a higher affinity for TF would result in greater targeting efficiency. This increase in affinity for TF would result in the ability to administer the TF targeted composition at lower concentrations as taught by Sorensen et al.

Garen teaches immunoconjugate proteins that consist of FVII and human IgG1 Fc and discloses a nucleic acid sequence that encodes FVII and human IgG1 Fc immunoconjugate, but Garen does not disclose the amino acid sequence of the resulting immunoconjugate protein. Translation of the nucleic acid immunoconjugate sequence disclosed by Garen as the "hfVIIasm immunoconjugate" indicates that this sequence contains 2 sequencing errors in the Fc region that result in premature stop codons. The sequence of human IgG1, and its use in fusion proteins was well known in the art at the time the invention was made as evidenced by Capon et al. (see entire document, particularly Figures 3, 4A, 4B1 and 4B2). As such, it would have been

obvious to a person of ordinary skill in the art at the time the invention was made to change the premature stop codons in the sequence of Garen to the wild type sequence of human IgG1 as taught by Capon et al. Motivation to make these changes comes from the teachings of Garen that utilize a full length immunoconjugate protein that contains the human IgG1 Fc region, such a full length protein not being obtainable from the disclosed nucleotide sequence of Garen without changing the sequence to remove the stop codons, with the changes being made to restore the sequence to that of wild type human IgG1 as taught by Capon. The protein expressed from this new construct that removes the premature stop codons would comprise SEQ ID NO:7 of the instant claims.

Further, for the reasons cited above, a person of ordinary skill in the art would have been motivated to make an additional change to remove the FVII active site mutation of Lys_{341} to Ala_{341} disclosed by Garen and coded for in his nucleic sequence labeled "hfVIIasm immunoconjugate" to restore the wild type sequence of human FVII. Such a change would allow for the binding of an active site inhibitor, thus increasing the affinity of the immunoconguate for TF which would allow for a more effective targeting of tumor cells that express TF as taught by Sorensen et al. Such modification of the nucleic acid sequence disclosed by Garen would yield a nucleotide sequence that encodes a protein that comprises SEQ ID NO:8 of the instant application.

8. Claims 1, 8, and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soule et al. (U.S. Patent No. 5,506,134, see entire document) in view of Kipriyanov et al. (Molecular Biotechnology, 12:173-201, see entire document).

The teachings of Soule et al. have been discussed above. These teachings differ from the claimed invention in that Soule et al. did not disclose the isotype of any of their monoclonal antibodies that are specific for FVII, and the monoclonal antibodies of Soule et al. are mouse and not human antibodies.

Kipriyanov et al. disclose that repeated dosages of mouse monoclonal antibodies to human patients induces an unwanted immune reaction known as HAMA (human antimurine antibody) (see entire document, particularly the first paragraph on page 173). Methods have been developed to address the immunogenicity of monoclonal antibodies include the use of chimeric, humanized and human antibodies. These forms of antibodies offer the advantage of being less immunogenic, and as such they are more suitable for administration to patients (see particularly the paragraph that spans pages 173 and 174). Kipriyanov et al. also teach that the isotype of the antibody molecule is important for determining *in vivo* effector function, with IgG1 being particularly desirable since it mediates antigen-dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (see particularly section 3.4, Choice of Constant Region, on page 176).

Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to make a fully human antibody from the antibodies disclosed by Soule et al. for the advantage of reducing the immunogenicity of the monoclonal

antibody as taught by Kipriyanov et al. A person of ordinary skill in the art would have been further motivated to make fully human antibodies with an IgG1 Fc region so that the antibody would have the advantageous properties of mediating ADCC and CDC as was also taught by Kipriyanov.

9. Claims 1 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garen, (WO 01/02439 A1, see entire document) in view of Holzer et al. (U.S. Patent No. 5,824,782, see entire document).

The teachings of Garen have been discussed above. These teachings differ from the claimed invention in that the composition of Garen does not contain a linker moiety that joins the FVII targeting domain to the IgG1 Fc effector domain.

Holzer et al. teaches methods for preparing immunoconjugates that consist of an effector molecule and a targeting element physically combined that are to be used in the treatment of tumors (see entire document, particularly column 1, lines 50-53). These elements are combined by an appropriate linker sequence that ensures the optimal binding of the conjugate to the target molecule (see particularly column 4, lines 55-58). Holzer further disclose the use of the peptide linker sequence $(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_x$ in making an immunoconjugate between a cytokine and an antibody C_H1 domain (see particularly column 12, lines 55-62).

Therefore, it would have been obvious to a person of skill in the art at the time the invention was made to modify the immunoconjugate of Garen to include a linker sequence. Motivation to make this modification comes from the disclosure of Holzer et

al. that linker sequences are used to ensure optimal binding of the conjugate to the target molecule. Claim 23 is included in this rejection because a 1 to 50 member straight or branched chain comprising carbon and at least one N, O, or S atom in the chain as recited in the Markush grouping is a description of a genus of molecules that includes peptides, such as Gly-Gly-Gly-Gly-Ser.

10. Claims 1, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garen, (WO 01/02439 A1, see entire document) in view of Rodwell et al. (U.S. Patent No. 4,671,958, see entire document).

The teachings of Garen have been described above. These teachings differ from the claimed invention in that the antibody immunostimulatory effector domain in the composition of Garen is not covalently coupled to the FVIIa polypeptide through oligosaccharides or sulfhydryl groups.

Rodwell et al. teach methods of conjugating proteins to antibodies for use in therapeutic methods (see entire document, particularly the abstract). Methods of attachment involving carbohydrate moieties and sulfhydryl groups are disclosed (see particularly sections 5.3.1 and 5.3.2, column 13 to column 16). The advantages of the chemical coupling methods disclosed by Rodwell et al. are that they maintain the antigen binding specificity of the antibody and maintain the ability of the antibody to activate complement while physically joining the protein and antibody together to increase the effective concentration of the compound at the target site (see particularly column 1, lines 45-57).

Therefore, it would have been obvious to a person of ordinary skill at the time the invention was made to use chemical coupling methods as taught by Rodwell et al. to join the antibody effector domain and the FVII polypeptide to make a TF targeting compound as taught by Garen. Motivation to do so comes from the disclosure of Rodwell et al. that their coupling methods allow for an increase of the effective concentration of a compound at the target site while maintaining antigen binding specificity and complement fixation capabilities. Note that the inclusion of a linker moiety is an optional requirement of the claims as currently recited.

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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